Environmental cues can reliably signal motivationally significant outcomes allowing them to be predicted and to inform appropriate behaviours. Neural activity in the orbitofrontal cortex (OFC) increases in the presence of reward predictive cues (Schoenbaum, Roesch, Stalnaker, & Takahashi, 2009; van Wingerden, Vinck, Lankelma, & Pennartz, 2010), suggesting that the OFC may form part of the representation of expected outcomes (Lucantonio et al., 2015; Rudebeck & Murray, 2014; Schoenbaum & Esber, 2010; Mark E Walton, Chau, & Kennerley, 2015). The OFC has been hypothesised as a site that integrates sensory and motivational information to adaptively increase or inhibit behaviour based on the up-to-the-moment expected value of predicted rewards (Rudebeck & Murray, 2014; Mark E Walton et al., 2015).

Surprisingly, disruption of OFC function does not disturb initial learning about cues that predict outcomes (Gallagher, McMahan, & Schoenbaum, 1999; M. A. McDannald, Lucantonio, Burke, Niv, & Schoenbaum, 2011) which is thought to depend on prediction-error signals that represent the discrepancy between expected and actual outcomes (Rescorla & Wagner, 1972; Schultz, 1998). Instead, current hypotheses attribute OFC involvement to situations in which initial learning must be modified by changes in the value or likelihood of the reward change. For example, in extinction procedures when an expected reward is no longer delivered the expected value of the cue should be updated to reflect this new state of affairs, a process that is predicted to involve OFC function (Panayi & Killcross, 2014; Wilson, Takahashi, Schoenbaum, & Niv, 2014). In line with this prediction, Panayi & Killcross (2014) found that selectively inactivating rodent OFC function during extinction results in abnormally persistent responding to a cue that no longer predicts reward across a number of days.

While impaired extinction following OFC inactivation (Panayi & Killcross, 2014) is consistent with the hypothesis that the OFC is required to update behaviour based on the current value of predicted rewards, there are two alternative explanations of these results. One possibility is that the OFC is involved in the formation of inhibitory associations between events and expected outcomes, and therefore the rats never learn to inhibit their established behaviour. In the past, inhibitory explanations of OFC function have been ruled out by evidence that subjects with OFC damage can learn to inhibit a response if it has not been learned already (E A Murray, O’Doherty, & Schoenbaum, 2007; Rudebeck, Saunders, Prescott, Chau, & Murray, 2013). However, suppression of behaviour can occur via a number of alternative mechanisms that do not involve inhibition per se, such as behavioural competition, attention, and habituation (Panayi & Killcross, 2014; Rudebeck et al., 2013). The objective of this work is to provide the first direct test of the role of the OFC in the acquisition of conditioned inhibitory associations.

Extinction learning has been argued to involve predominantly new context-dependent inhibitory learning rather than unlearning of the original association (Bouton, 1993; Delamater, 2004). Therefore, a second explanation of the role of the OFC in extinction learning is the formation of new state information to support this new inhibitory learning (Wilson et al., 2014). In the absence of this new state representation Wilson et al (Wilson et al., 2014) predict that the rate of extinction will be retarded since the original association will undergo unlearning rather than the formation of new context specific inhibitory learning. Importantly, the OFC is proposed to only be involved in the representation of task states when the states are not explicitly signalled but instead require the use of memory to infer a new state.

Considered together, these hypotheses of OFC function provide three distinct predictions about the role of the OFC in the acquisition and expression of inhibitory associations in a Pavlovian conditioned inhibition task. If the OFC is simply involved in the acquisition of inhibitory associations, then OFC inactivation should disrupt the expression and subsequent learning of conditioned inhibition. If the OFC is involved in modulating behaviour based on the current expected value of predicted outcomes, then OFC inactivation should disrupt the expression but not necessarily the acquisition of a conditioned inhibitor. Finally, if the OFC is necessary for representing task states when changes in task contingencies are not explicitly signalled, then OFC inactivation should not disrupt the expression or acquisition of an explicitly signalled conditioned inhibitor. Our findings indicate that OFC inactivation impairs the selective expression of behavioural inhibition during task acquisition. However, conditioned inhibition is acquired in rats when subsequently tested with functional OFC. A second experiment assessed the role of this form of conditioned inhibition in extinction learning with parameters comparable to those of (Panayi & Killcross, 2014). Our findings suggest that the OFC is not simply involved in the acquisition of inhibitory associations, but instead modulates behaviour based on expected outcomes.

**Materials and Methods**

*Animals.* Fifty-six adult male Long-Evans rats (302-406 g prior to surgery; Monash Animal Services, Gippsland, Victoria, Australia) were used (experiment 1, N = 32; experiment 2, N = 24). Rats were housed four per cage in ventilated Plexiglass cages in a temperature regulated (22 ± 1­°C) and light regulated (12h light/dark cycle, lights on at 7:00 AM) colony room. At least one week prior to behavioural testing, feeding was restricted to ensure that weight was approximately 95% of ad libitum feeding weight, and never dropped below 85%. All animal research was carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratories Animals (NIH publications No. 80-23, revised 1996) and approved by the University of New South Wales Animal Care and Ethics Committee.

*Apparatus.* Behavioural testing was conducted in eight identical operant chambers (30.5 x 32.5 x 29.5 cm; Med Associates) individually housed within ventilated sound attenuating cabinets. Each chamber was fitted with a 3-W house light that was centrally located at the top of the left-hand wall. Food pellets (45 mg dustless precision grain-based pellets; Bio-serv, Frenchtown, NJ, USA) could be delivered into a recessed magazine, centrally located at the bottom of the right hand wall. The top of the magazine contained a white LED light that could serve as a visual stimulus. Access to the magazine was measured by infrared detectors at the mouth of the recess. Two retractable levers were located on either side of the magazine on the right-hand wall. A speaker located to the right of the house light could provide auditory stimuli to the chamber. In addition, a 5-Hz train of clicks produced by a heavy-duty relay placed outside the chamber at the back right corner of the cabinet was used as an auditory stimulus. The chambers were wiped down with ethanol (80% v/v) between each session. A computer equipped with Med-PC software (Med Associates Inc., St. Albans, VT, USA) was used to control the experimental procedures and record data.

Locomotor activity was assessed in a set of 4 rat open field arenas (Med Associates Inc., St. Albans, VT, USA) individually housed in light and sound attenuating cabinets. A 3-W light attached on the top left corner of the sound attenuating cabinet provided general illumination in the chamber and was always on. A 28 V DC fan on the right hand wall of the sound attenuating cabinet was also left on throughout testing to mask outside noise. The floor of the open field arena was smooth plastic and the four walls were clear Perspex with a clear Perspex roof containing ventilation holes. The internal dimensions of the chamber were 43.2 x 43.2 x 30.5 cm (length x width x height).Two opposing walls contained an array of 16 evenly spaced infrared detectors set 3 cm above the floor to detect animal locomotor activity. A second pair of infrared beam arrays was set 14 cm above the floor on the remaining walls to detect rearing behaviours. Infrared beam breaks were recorded using a computer equipped with Activity Monitor software (Med Associates Inc., St. Albans, VT, USA) which provided a measure of average distance travelled based on beam break information.

*Surgery.* Surgery was performed prior to training in experiment 1 and after initial training in experiment 2.Bilateral guide cannulae were surgically implanted targeting the lateral OFC. Rats were anesthetized with isoflurane, their heads shaved, and placed in a stereotaxic frame (World Precision Instruments, Inc., Sarasota, FL, USA). The scalp was incised, and the skull exposed and adjusted to flat skull position. Two small holes were drilled for the cannulae using a high-speed drill, and four holes were hand drilled on different bone plates to hold fixing screws. Bilateral stainless steel guide cannulae (26 gauge, length 5mm below pedestal; Plastics One, Roanoke, VA, USA) were lowered into the lateral OFC (AP: +3.5 mm; ML: ±2.2 mm; D-V: -4.0 mm from bregma). Cannulae were held in place by dental cement and anchored to the skull with 4 fixing screws. Removable dummy cannulae were inserted into the guide cannulae to prevent them from blocking. After one week of postoperative recovery, rats were returned to food restriction for 2 days prior to further testing.

*Drugs and infusions.* The GABAA agonist muscimol (Sigma-Aldrich, Switzerland) was dissolved in 0.9% (w/v) non-pyrogenic saline to obtain a final concentration of 0.5 *μ*g/0.5 *μ*l. Non-pyrogenic saline 0.9% (w/v) was used as the saline control.During infusions, muscimol or saline was infused bilaterally into the lateral OFC by inserting a 33 gauge internal cannula into the guide cannula which extended 1 mm ventral to the guide tip. The internal cannula was connected to a 25 *μ*l glass syringe (Hamilton Company, Reno, NV, USA) attached to a microinfusion pump (World Precision Instruments, Inc., Sarasota, FL, USA). A total volume of 0.5 *μ*l was delivered to each side at a rate of 0.25 *μ*l/min. The internal cannula remained in place for an additional 1 min after the infusion and then removed. During the infusion procedure animals were allowed to move freely in a bucket to minimize stress. Dummy cannulae were removed prior to, and replaced immediately after, infusions. For the two training sessions prior to infusions, all animals received dummy infusions which were identical to the infusion procedure, but no liquids were infused. These dummy infusions were performed to familiarize the rats with the microinfusion procedure and thereby minimize stress.

*Histology.* Following completion of behavioural testing, rats received a lethal dose of sodium pentobarbital. Brains were extracted, frozen, and sectioned coronally at 40 *μ*m through the lateral OFC with a cryostat. Every third section was collected on a slide and stained with cresyl violet. The location of cannula tips was determined under a microscope by a trained observer, unaware of subject’s group designations, using the boundaries defined by the atlas of George Paxinos and Watson (1998). Rats with bilateral cannulae placements outside the lateral or dorsolateral OFC were excluded from statistical analyses.

*Magazine training.* Prior to each experiment, all rats were familiarised with retrieving rewards from the magazine in a session of magazine training that lasted approximately 32 mins. Rewards, consisting of two pellets delivered 0.25s apart, were delivered randomly throughout the session every 120s until 32 pellets were delivered. The house light was kept illuminated throughout the session.

*General session parameters.* All sessions consisted of a number of trials in which 10s auditory and/or visual cues (conditioned stimuli; CS) were presented. Visual cues designated as X and Y were flashing panel lights (0.1 s illuminated, 0.1s off) or extinguishing the house light (identity counter balanced). Visual cue Z was always a flashing magazine light (0.1 s illuminated, 0.1s off) for all animals. Auditory cues A and B were a 5 Hz train of clicks or a 78 dB white noise (identity counter balanced). Auditory cue C was always an 84 dB, 2.6 kHz tone. On rewarded trials (denoted by the symbol ‘+’) a single reward pellet was delivered upon CS termination. On non-reinforced trials (denoted by the symbol ‘-’), no reward was delivered. The variable inter-trial-interval was 90s (± 45s). Unless stated, only a single training session occurred per day and cue order was randomised. All animals were handled in the infusion bucket for 5 minutes prior to each session and handled similarly regardless of whether drug infusions were administered. This was done to equate handling cues and stress on all training days.

*General experimental design.* Experiments 1 and 2 were designed to establish cue X as a conditioned inhibitor (*Figure 1A and 2A*). This was achieved by first training cue A as a valid predictor of reward (A+, Stage 1) before training the compound AX as a valid predictor of the absence of reward (AX-, Stage 2). Experiment 1 was designed such that A+ and AX- were trained as a discrimination within the same sessions, a feature negative discrimination procedure that is commonly used to generate robust conditioned inhibition to cue X (Papini & Bitterman, 1993). Experiment 2 was designed such that AX- was presented in separate sessions only after A+ was well trained instead of within the same session. This design has been used to probe the formation of conditioned inhibition in extinction procedures (Rescorla, 1979), and provided a test of whether the extinction parameters employed by (Panayi & Killcross, 2014) promoted the formation of conditioned inhibition.

Experiments 1 and 2 employed both a summation and a retardation test to assess whether cue X had become a conditioned inhibitor (Rescorla, 1969). Briefly, a cue can be considered to be a conditioned inhibitor if it is able to transfer its inhibitory properties to other predictive cues (summation test), and it should be harder to transform an inhibitory cue into an excitatory cue relative to a neutral cue (retardation test). In summation tests, cue X is presented in compound with another excitatory cue, BX, and if responding is inhibited/lower to this compound than to B alone, then cue X is considered to be a conditioned inhibitor. However, it is possible that lower responding to the compound BX in a summation test is caused by generalisation decrement i.e. a reduction in responding due to generalisation between compound AX and BX, or due to external inhibition caused by the novel pairing of cues B and X. Alternatively, in a retardation test, if X has accrued inhibitory properties, the rate of acquisition to cue X will be lower than acquisition to a novel. Unlike summation tests, there is no issue of generalization decrement in a retardation test, however slower acquisition to cue X may be caused by reductions in attention to cue X as it is presented repeatedly during AX- training (i.e. latent inhibition). A consistent attentional explanation of both the summation and retardation test is not possible. It has therefore been argued that to rule out alternative explanations, both summation and retardation tests are needed to establish that cue X has acquired conditioned inhibitory properties (Papini & Bitterman, 1993).

*Experiment 1 acquisition days 1-4.* During each acquisition session a total of 36 trials were presented consisting of 12 A+, 12 B+ and 12 Z+ trials. Each session lasted 60 mins. On days 3 and 4, all animals received dummy infusions immediately prior to the session.

*Experiment 1 feature negative training days 5-10.* During each feature negative training session all animals received a total of 36 trials consisting of 10 A+, 20 AX- and 6 Z+ trials. The non-rewarded AX- trials consisted of the simultaneous presentation of the audio-visual cues A and X. The A+/AX- feature negative discrimination was used to establish cue X as a conditioned inhibitor. Prior to each feature negative training session all animals received an infusion of either muscimol or saline targeting the OFC.

*Experiment 1 cue retraining days 11-12.* During cue retraining sessions a total of 36 trials were presented, consisting of 18 B+ and 18 Z+ trials. This retraining was done to ensure that responding to cue B was high prior to the summation test and to assess any persistent effects of the infusion procedure.

*Experiment 1 summation probe test day 13.* The summation probe test consisted of 27 trials (45 mins session length) in the following order: first 3 Z+ and 3 B+ trials (order: Z+, B+, B+, Z+, B+, Z+). This rewarded start ensured high responding to the critical target cue B. Then 2 B- and 2 BX- trials were presented, followed by a Z+ trial. This cycle of 5 trials (B-/BX-/Z+) was repeated 2 more times. The B-/BX- cues were probe trials to test whether cue X had acquired inhibitory properties that transferred to cue B. Rewarded Z+ trials were interspersed throughout the session to maintain responding throughout the probe trials. Finally, all animals received 6 presentations of Y- at the end of the session. This pre-exposure to cue Y was done to minimise any external inhibition that may occur during the retardation test that followed.

*Experiment 1 retardation test days 14-16.* The retardation test sessions contained 36 trials consisting of 12 X+, 12 Y+ and 12 Z- trials (order randomized). This test shows whether the prior inhibitory training with cue X impairs subsequent excitatory acquisition relative to the novel cue Y. The non-rewarded cue Z was designed to prevent animals from responding non-discriminatively to all cues during this acquisition session.

*Experiment 1 consumption test days 17-18.* Following the retardation test, all animals were given a consumption test to assess whether muscimol infusions into the OFC impaired the motivation or timing of pellet consumption, which may explain reduced performance during the Stage 2 feature negative training following infusions. On day 17, all animals were given a dummy infusion immediately prior to entering the test chamber. Prior to the session, 40 pellets were placed in the magazine. All animals were given 30 minutes in the chamber. Magazine behaviour was recorded during this session for analysis, but there were no programmed events throughout the session. On day 18 all animals were infused with muscimol or saline before being entered for a second consumption test identical to that on day 17.

*Experiment 2 acquisition days 1-9.* During acquisition sessions there were a total of 36 trials, consisting of 9 A+, 9 B+, 9 C+ and 9 Z+ trials. Each session lasted 60 mins. Animals were entered for 2 sessions per day for stage 1 training for a total of 12 sessions across days 1-6. Animals were then returned to free feeding and surgery was performed. Immediately following post-operative recovery all animals were returned to food restriction 2 days prior to further acquisition. Post-operative acquisition on days 7-9 were identical to pre-surgical Stage 1 acquisition, except that only a single session was administered per day. On the final two days all animals received dummy infusions immediately prior each session.

*Experiment 2 feature negative training days 10-13.* During the feature negative training, each session consisted of 36 trials such that there were 18 AX- and 18 C- trials. Infusions of saline or Muscimol were administered immediately to separate groups (matched on performance to all cues) prior to each of these sessions.

*Experiment 2 extinction test day 14.* During the extinction test there were a total of 24 trials consisting of 12 A- and 12 C- trials.

*Experiment 2 summation and retardation tests*. The summation and retardation tests were identical to those described in Experiment 1.

*Experiment 2 Locomotor activity.* At the end of training, animals were locomotor screened following an additional drug infusion (either saline or Muscimol) to evaluate whether drug infusions affected general activity levels between groups.

Data analysis. CS responding was operationalized as the number of magazine entries during the 10s CS. PreCS responding was operationalized as the frequency of responding during the 10s immediately preceding the 10s CS and was used as a measure of baseline responding to the testing context. All data were analysed with mixed ANOVAs, and significant interactions of interest were followed up with ANOVAs on the relevant subset of data. Following significant omnibus ANOVA tests, planned linear and quadratic orthogonal trend contrasts and their interactions between groups were analysed to assess differences in rates of responding.

For convenience, cue Z was analysed separately in all stages as it was a control cue that was not counterbalanced (a flashing light in the magazine) and elicited a different pattern of responding to the other cues.

**Results**

**Experiment 1: OFC inactivation disrupts the expression but not the acquisition of conditioned inhibition**

*Histology*

Cannulae placements are depicted in Figure 1B. Two animals were excluded from further analysis due to misplaced cannulae. During training a further two animals assigned to the saline group were excluded and were not trained further as they failed to acquire magazine training after several days. Final numbers for infusion groups in Experiment 1 were saline (n = 13) and muscimol (n = 15).

Baseline responding

Rates of baseline responding during the 10s PreCS period did not significantly differ between groups during any of the testing phases, and justified the analysis of CS-PreCS difference scores as measures of discriminative responding to the cues in subsequent analyses. Briefly, Group x Day mixed ANOVAs were run separately for each stage of testing. During stage 1 acquisition (main effect of Group F(1, 26) = 3.20, *p* = .09; Group x Day interaction F(3, 78) = 1.47, *p* = .23), stage 2 feature negative training, stage 3 cue re-training, summation and retardation tests all Group and Group x Day interactions failed to reach significance (all F < 2.01, *p* > .16).

*Stage 1: Acquisition (Days 1-4)*

Prior to drug infusions, both groups acquired discriminative responding to cues A and B at similar rates (data not shown). This impression was confirmed by a mixed ANOVA with main factors of Group (saline, muscimol), Cue (A, B) and Day (1-4). Acquisition of responding to cues A and B increased significantly (main effect of day F(3, 78) = 20.41, *p* < .001; significant linear trend across Day F(1, 26) = 37.33, *p* < .001) and did not differ between groups (all other effects F < 1.5, *p* >.23).

Similarly, responding to control cue Z (Figure 2, stage 1) did not differ between groups, nor did it increase across Day (main effect of Group, Day and Group x Day interaction, all (all *F* < 1.6, *p* > .21). However, overall discriminative responding to cue Z was significantly above PreCS levels (test of model intercept, *F*(1, 26) = 24.17, *p* < .001). Therefore, at the end of stage 1, all animals had acquired discriminative responding to all cues, but responding was significantly lower to cue Z.

*Stage 2: OFC inactivation abolishes selective inhibition of behaviour (days 5-10)*

The saline group successfully acquired the feature negative A+/AX- discrimination by increasing responding to the rewarded cue (A+) and selectively inhibiting responding to the non-rewarded compound (AX-). Muscimol infusions into OFC completely abolished the acquisition of this discrimination and resulted in equivalently low levels of responding to both A+ and AX- (Figure 1C). This impression was confirmed by a Group x Cue (A+, AX-) x Day (6 days) mixed ANOVA. The analysis revealed a significant 3-way Group x Cue x Day interaction (*F*(5, 130) = 2.89, *p* = .02; and a significant Group x Cue interaction *F*(1, 26) = 8.12, *p* = .008) suggesting that there were group differences in acquisition of the feature negative discrimination across days. Follow up Cue x Day ANOVAs were conducted separately for each group to explain this interaction. The muscimol group increased responding to the cues across days (main effect of Day, *F*(5, 70) = 4.88, *p* = .001; linear trend *F*(1, 14) = 11.66, *p* = .004) but did not reliably discriminate between cues (non-significant effect of Cue and Cue x Day interaction, all *F*<1, *p* > .86). In contrast, the saline group acquired greater responding to A+ than AX- as suggested by significant effects of Cue (*F*(1, 12) = 11.13, *p* = .006), Day (*F*(5, 60) = 7.84, *p* < .001), and a Cue x Day interaction (*F*(5, 60) = 5.95, *p* < .001). Specifically, in the saline group responding to A+ increased (linear trend *F*(1, 12) = 28.04, *p* < .001), whereas responding to AX- did not significantly increase across days (linear trend *F*(1, 12) = 2.68, *p* = .13). Therefore, the saline group showed behavioural evidence of selective inhibition during the feature negative discrimination which was abolished by intra-OFC infusions of muscimol. While this suggests that OFC function is necessary for selective inhibitory control of behaviour, it is unclear whether learning about the conditioned inhibitor X was also impaired.

*Stage 3: Retraining (days 11-12)*

In stage 3, the overall suppression of responding observed in stage 2 persisted temporarily during retraining to cue B drug-free (Figure 1D). This was confirmed by a Group x Day (11, 12) mixed ANOVA which revealed that responding to cues increased across days (main effect of Day, *F*(1, 26) = 22.37, *p* = .001). Furthermore, a main effect of Group *F*(1, 26) = 4.59, *p* = .04) and a Group x Day interaction (*F*(1, 26) = 4.23, *p* = .05) revealed group differences in responding to cue B. Simple effects revealed that the muscimol group responded significantly lower than the saline group on day 11 (*F*(1, 26) = 7.52, *p* = .01) but not day 12 (*F*(1, 26) = 1.86, *p* = .19). This suggests that the effect of muscimol infusion in stage 2 temporarily and non-selectively lowered overall performance when trained drug free in stage 3. It is possible that this effect is due to the disruption of motivation for the reward or an overall suppression of motor function, however these possibilities were ruled out by the results of the consumption test administered at the end of testing (reported below).

*Summation and retardation test: OFC inactivation during training does not prevent the acquisition of conditioned inhibition (days 13-16)*

While OFC inactivation successfully abolished the expression of selective conditioned inhibition in the feature negative discrimination (stage 2), it is not clear whether this indicates a failure of acquisition of conditioned inhibition or just impaired behavioural expression. To address this question directly, summation and retardation tests of conditioned inhibition (Papini & Bitterman, 1993; Rescorla, 1969) were administered drug-free to allow for any latent learning to be expressed.

The results of the summation test (*F*igure 1E) revealed that both groups respond less to the compound BX- than B- which suggests that cue X successfully acquired inhibitory properties during the feature negative training (stage 2). This observation was confirmed by a Group x Cue (B-, BX-) mixed ANOVA. Specifically, there was a significant main effect of Cue (*F*(1, 26) = 7.60, *p* = .01). While the magnitude of the Cue effect may appear weaker in the muscimol group than the saline group (visual inspection of figure 1E), this observation was not supported statistically (no main effect of Group *F*(1, 26) = 0.72, *p* = .40, or Group x Cue interaction *F*(1, 26) = 2.12, *p* = .16). These findings suggest that intra-OFC infusions of muscimol did not disrupt the acquisition of conditioned inhibition to cue X as assessed by a summation test. However, a reduction in responding to the BX compound could also be explained by enhanced attention to cue X, generalisation decrement, or external inhibition. To rule out these alternative explanations a retardation test was conducted in which the rate of acquisition to X+ was compared to the relatively novel cue Y+. If cue X has acquired inhibitory properties, then acquisition should be slower to X+ than Y+. Importantly, this result would be incompatible with an account of the summation test appealing to enhanced attention to X, which would predict an increase in the rate of learning.

During the retardation test (days 14-16) acquisition to target cue X+ appeared significantly lower than control cue Y+ in both groups (Figure 1F). A Group x Cue (X+, Y+) x Day (14, 15, 16) mixed ANOVA revealed a significant main effect of Cue (*F*(1, 26) = 8.82, *p* = .006) and Day (*F*(2, 52) = 5.53, *p* = .008) but no other significant effects (Cue x Day interaction *F*(2, 52) = 2.22, *p* = .12, all other *F*< 1.42, *p* > .24). This retarded acquisition to cue X+ relative to Y+ suggests a significant retardation effect of similar magnitude in both the saline and muscimol groups. Together, the results of the summation and retardation tests suggest that cue X has indeed acquired conditioned inhibition, even though OFC inactivation abolished discriminative performance during the feature negative training in stage 2.

*Control cue Z: OFC inactivation disrupts Pavlovian acquisition*

The adverse consequences of disrupting OFC function are usually only detected when task contingencies change (Rudebeck & Murray, 2014; Wilson et al., 2014), but rarely during the initial acquisition of a task when contingencies and response requirements remain constant (M E Walton, Behrens, Noonan, & Rushworth, 2011). Therefore, it is surprising that OFC inactivation during the feature negative discrimination also disrupted the acquisition of responding to control cue Z (Figure 2, Stage 2). This impression was confirmed by a significant main effect of Group (*F*(1, 26) = 16.46, *p* < .001) and a Group x Day interaction (*F*(5, 130) = 3.47, *p* = .006; Group x Day linear trend contrast *F*(1, 26) = 6.27, *p* = .02). Follow up linear trend contrasts across Day revealed significant increases in responding in the saline group (*F*(1, 12) = 18.97, *p* = .001) but not the muscimol group (*F*(1, 14) = 3.26, *p* = .09; overall muscimol group responding remained significantly above baseline *F*(1, 14) = 22.37, *p* < .001). Therefore, muscimol infusions significantly suppressed acquisition to cue Z, which suggests a role for OFC in Pavlovian acquisition.

Suppressed responding to cue Z persisted in the muscimol group when trained drug-free in subsequent sessions. Drug-free acquisition to cue Z (Figure 2, Stage 3) was assessed with a Group x Day (11, 12) mixed ANOVA which revealed that responding to cues increased across days (main effect of Day, *F*(1, 26) = 4.24, *p* = .05). Furthermore, a significant main effect of Group *F*(1, 26) = 7.17, *p* = .01) but no significant Group x Day interaction (*F*(1, 26) = 0.31, *p* = .58) revealed that responding to cue Z was significantly lower in the muscimol than the saline group. This difference between groups in responding to cue Z persisted across three days of extinction to cue Z during the retardation test (Figure 2, Extinction). A Group x Day mixed ANOVA supported this interpretation with a significant main effect of Group (*F*(1, 26) = 4.50, *p* = .04) and Day (*F*(2, 52) = 27.44, *p* < .001) but no Group x Day interaction (*F*(2, 52) = 1.80, *p* = .18). However, it is likely that this group difference in extinction is the result of the pre-existing differences in responding at the end of stage 3. Overall, the pattern of data suggests that muscimol inactivation of OFC disrupts both learning and behaviour of simple Pavlovian cue-outcome associations.

*OFC inactivation does not disrupt the motivation to consume food reward*

The significant suppression of responding to al cues following OFC inactivation observed in stage 2 may have been a consequence of reduced motivation to consume the food reward. This explanation is unlikely given the absence of uneaten rewards following sessions in stage 2, however a more direct test of this explanation was necessary to rule out the possibility that the rewards were not eaten towards the end of the session when muscimol was no longer effective. Therefore, a consumption test was conducted within the test chambers with all animals being tested 10 mins after an infusion to ensure that the muscimol was maximally effective. Prior to the consumption test one muscimol and two saline group rats lost their cannula assembly and were not eligible for testing (saline n = 11, muscimol n = 14). All animals consumed all pellets by the end of the session on both days, regardless of infusion group. Similarly, there was no evidence that muscimol infusion differentially affected magazine approach for reward. A Group x Infusion (No Infusion, Infusion) x Block (6 blocks of 5 mins) mixed ANOVA found no significant main effect or interactions with Group (all *F* < 1.00, *p* > .34). A main effect of Block (*F*(5, 115) = 246.18, *p* < .001), Infusion (*F*(1, 23) = 6.53, *p* = .02), and Block x Infusion interaction (*F*(5, 115) = 2.69, *p* = .02), revealed that overall responding was lower on infusion day 18. These findings suggest that the low level of responding to all cues in stage 2 following muscimol infusions is unlikely to be due to suppressed appetite or motivation for the US, or a general suppression of response vigour.

**Experiment 2: OFC inactivation does not disrupt Pavlovian extinction learning by impairing the acquisition of conditioned inhibition**

Histology

Cannulae placements are depicted in Figure 3B. All cannulae tips were located within LO or DLO. Final group numbers were saline (n = 12) and muscimol (n = 12).

Baseline responding

Rates of baseline responding did not significantly differ between groups during any of the testing phases and justified the analysis of CS-PreCS difference scores as measures of discriminative responding to the cues in consequent analyses. Briefly, one-way Group or Group x Day mixed ANOVAs were run separately for each stage of testing to assess the effects of Group. During stage 2 feature negative training (main effect of Group *F*(1, 22) = 2.55, *p* = .12; Group x Day interaction *F*(3, 66) = 1.72, *p* = .17), stage 3 testing (Group *F*(1, 22) = 3.32, *p* = .08), during stage 1 acquisition, summation and retardation tests all Group and Group x Day interactions failed to reach significance (all *F* < 1.72, *p* > .17).

*Stage 1: Acquisition (days 1-9)*

Acquisition of discriminative responding to cues A, B and C did not differ between (infusion) groups across stage 1 of acquisition. A Group x Cue (A, B, C) x Day mixed ANOVA revealed a significant main effect of Day (*F*(8, 176) = 26.07, *p* < .001) but no significant effects of Cue, Group or their interactions (all *F* < 1, *p* > .65). Therefore, acquisition was successful to all cues and did not differ between groups.

*Stage 2: OFC inactivation enhances within- but disrupts between session Pavlovian extinction (days 10-13)*

Extinction of cue C following infusions in stage 2 allowed for a replication of the findings of (Panayi & Killcross, 2014) that OFC inactivation disrupts between- but not within- session extinction. Extinction to cue A in compound with cue X was designed to test whether OFC inactivation impairs Pavlovian extinction by disrupting the formation of conditioned inhibition that may form during extinction (Delamater, 2004; Rescorla, 1969). Overall, the rate of extinction differed between drug infusion groups (*F*igure 3C) such that behaviour in the muscimol group appeared to extinguish more rapidly within-session but not between-sessions compared to the saline group. A mixed Group x Cue (AX-, C-) x Day (4) x Block (3 blocks of 6 trials) ANOVA supported the observed pattern of results.

In both groups, evidence of extinction between- and within-sessions was supported by significant main effects of Day (*F*(3, 66) = 17.65, *p* < .001) and Block (*F*(2, 44) = 24.40, *p* < .001) and a Day x Block interaction (*F*(6, 132) = 2.52, *p* = .02). Overall responding to both cues did not differ (non-significant main effect of Cue *F*(1, 22) = 1.69, *p* = .21) but a significant Cue x Day interaction suggested that extinction between days was more rapid for AX- than C- (an effect that did not differ between groups, non-significant Group x Cue x Day interaction *F*(3, 66) = 0.83, *p* = .48). Follow up analysis of cue differences revealed a significant Cue x Day linear trend interaction *F*(1, 22) = 8.41, *p* = .01, such that the magnitude of significant negative trend across days was greater for C- (*F*(1, 22) = 33.17, *p* < .001) than AX- (*F*(1, 22) = 7.77, *p* = .01). Reduced responding to the compound AX- compared to C- is consistent with external inhibition or generalisation decrement accounts of the novel presence of cue X suppressing responding.

While there was no overall effect of Group (*F*(1, 22) = 0.63, *p* = .44) there was a significant Group x Day (*F*(3, 66) = 2.93, *p* = .04) and a Group x Block interaction (*F*(2, 44) = 16.35, *p* < .001; all other interactions with Group failed to reach significance, all *F* < 2.30, *p* > .11). Follow up analysis of linear and quadratic Group x Day trend interactions failed to reach significance (linear *F*(1, 22) = 3.44, *p* = .08, quadratic *F*(1, 22) = 3.05, *p* = .10). This suggests that the impaired between-session extinction observed in the muscimol group only approached significance. Follow up analysis of linear and quadratic Group x Block trend interactions were significant (linear *F*(1, 22) = 34.64, *p* = .001; quadratic *F*(1, 22) = 20.94, *p* < .001). Simple trend contrasts across Block revealed significant linear and quadratic trend for the muscimol group (linear *F*(1, 11) = 14.69, *p* = .003, quadratic *F*(1, 11) = 5.08, *p* = .046) but only significant linear trend in the saline group (linear *F*(1, 11) = 21.73, *p* = .001, quadratic *F*(1, 11) = 01, *p* = .93). This pattern of results suggests that the linear decrease in within-session extinction was greater in the muscimol group compared to the saline group. This greater linear increase in the muscimol group is likely to be due to higher responding at the start of each session in the muscimol group, whereas the lower responding in the saline group at the start of each session provided less opportunity for any further reduction in responding.

To directly assess impairments the retention of extinction between-sessions a Group x Cue x Day analysis was run on the first block of trials only (Panayi & Killcross, 2014). This analysis revealed a significant main effect of Day (*F*(3, 66) = 10.19, *p* < .001), a Cue x Day interaction Day (*F*(3, 66) = 2.88, *p* = .04) and a significant main effect of Group (*F*(1, 22) = 4.46, *p* < .05). This suggests that there was evidence of between-session extinction in both the saline and the muscimol groups, however overall responding was higher in the muscimol group. Therefore, there is some evidence of poorer between-session extinction retention in the muscimol group compared to the saline group.

*Stage 3 Extinction test (Day 14)*

Drug free tests of A- and C- revealed that the muscimol group did not acquire extinction to both cues to the same extent as the saline group (Figure 3D). Surprisingly, there was no evidence that compound extinction of cue A with cue X had “protected” cue A from extinction relative to cue C, in fact the mean responding to both cues were identical in both groups. A mixed Group x Cue (A-, C-) x Block (4 blocks of 3 trials) ANOVA supported this observation with no significant effect of Cue or Group x Cue interaction (both *F*(1, 22) = 0.00, *p* = 1.00). However, there was a significant effect of Block (*F*(3, 66) = 3.45, *p* = .02) suggesting within-session extinction behaviour at test and a significant main effect of Group (*F*(1, 22) = 16.02, *p* = .001) showing higher responding in the muscimol than the saline group (all other effects did not reach significance, all *F* < 1.38, *p* > .26). Impaired retention of extinction to cue C in the muscimol group when tested drug free successfully replicates the findings of (Panayi & Killcross, 2014) showing that OFC inactivation disrupts extinction learning.

*Stage 4 Summation test (Day 15)*

Responding to compound BX was lower than to cue B alone in both groups at test (Figure 3E). A Group x Cue (B-, BX-) mixed ANOVA supported this with a significant main effect of Cue (*F*(1, 22) = 4.67, *p* = .04) but no significant effect of Group (*F*(1, 22) <.01, *p* = .96) or Group x Cue interaction (*F*(1, 22) = 0.10, *p* = .75). Therefore, the summation test provided evidence of conditioned inhibition to cue X in both groups.

Stage 5 Retardation test (Days 16-18)

Responding during the retardation test suggested that the rate of acquisition to cue Y was greater than cue X in the muscimol group but not the saline group (Figure 3F). However, this observation was not fully supported statistically by a Group x Cue (X, Y) x Day mixed ANOVA which failed to reveal a significant Group x Cue x Day 3-way interaction (*F*(2, 44) = 2.23, *p* = .12; there was a significant main effect of Day *F*(2, 44) = 10.87, *p* < .001, but all other effects failed to reach significance, all *F* < 2.68, *p* > .12). Given the weak evidence for conditioned inhibition in this experimental design in the literature (Rescorla, 1979), planned orthogonal linear and quadratic Group x Cue x Day trend contrasts were tested. This planned analysis revealed a significant quadratic (*F*(1, 22) = 5.42, *p* = .03) but not linear (*F*(1, 22) = 0.68, *p* = .42) 3-way interaction. Follow up Cue x Day quadratic trend was found to be significant in the muscimol group (*F*(1, 11) = 7.53, *p* = .02) but not the saline group (*F*(1, 11) = 0.14, *p* = .71). This suggested that the rate of increase during acquisition was greater for cue Y than cue X in the muscimol but not the saline group.

Control cue Z

Responding to control cue Z did not differ throughout training (data not shown). For completeness, responding during acquisition to cue Z did not differ between groups in stage 1. A mixed Group x Day(1-9) ANOVA supported this observation revealing only a main effect of day (*F*(8, 176) = 8.80, *p* < .001) but no main effect of Group or Group x Day interaction (all *F* < 0.18, *p* > .99). The rate of extinction to control cue Z during the retardation test did not differ between groups as confirmed by a mixed Group x Day(16, 17, 18) ANOVA with no significant effect of Group (*F*(1, 22) = 2.07, *p* = .16) or Group x Day interaction (*F*(2, 44) = 0.08, *p* > .93; significant main effect of Day *F*(2, 44) = 20.78, *p* < .001).

*OFC inactivation does not impair spontaneous locomotor activity*

To test whether the rapid within-session extinction observed following muscimol infusions in stage 2 were the result of general suppression of locomotor activity, a spontaneous locomotor activity test was conducted. There was no differential effect of drug infusion on general locomotor activity. This was supported by a mixed Group x Block (6 blocks of 10 mins) ANOVA on total ambulatory distance which revealed a significant effect of Block (*F*(5, 110) = 93.52, *p* < .001) but no Group or Group x Block interaction effects (all *F* < 1, *p* > .96).

**Discussion**

Our results reveal a selective role for the OFC in inhibitory behavioural control, which partially support the traditional hypothesis of OFC function as a source of inhibitory control over well-established behavioural responses. However, despite the abolition of selective inhibitory behavioural control following OFC inactivation, OFC function was not necessary for the underlying learning of an inhibitory association, as assessed by summation and retardation tests. This suggests that the learning and subsequent expression of conditioned inhibition are neutrally dissociable. This dissociation between learning and behaviour following lateral OFC inactivation in rodents is broadly consistent with recent findings in monkeys (Elisabeth A Murray, Moylan, Saleem, Basile, & Turchi, 2015) and in humans (Bechara, Damasio, Damasio, & Anderson, 1994; Fellows, 2011), which suggest that updating expected outcome values and translating this knowledge into behaviour can be dissociated within OFC subregions.

The fundamental impairment in behavioural control following OFC inactivation in the present studies cannot simply be attributed to failed inhibitory control as there were multiple instances of enhanced behavioural inhibition following OFC inactivation. Firstly, OFC inactivation in experiment 1 disrupted the behavioural discrimination by suppressing responding to both the rewarded cue (A+) and the non-rewarded compound (AX-). Secondly, this impairment in increasing responding was also observed with the acquisition of responding to control cue Z+ in experiment 1. Finally, experiment 2 found evidence of enhanced behavioural inhibition within extinction sessions following OFC inactivation. Thus, an account of the OFC as the neural locus of learning inhibitory associations, or even general inhibitory behavioural control, does not effectively describe the bidirectional disruption of behavioural control observed in the present studies.

This conclusion is consistent with population and single-unit neuronal activity recordings in the rodent OFC. For example, in a stop-signal task that requires the use of cues to guide correct behaviour (Bryden & Roesch, 2015), OFC activity is sensitive to the direction of responding and this activity is enhanced when the observed behaviour required suppression of an alternative response. This suggests that the OFC is involved in inhibitory behavioural tasks because it plays a role in guiding and boosting behavioural control of correct/chosen responses rather than the inhibition of incorrect responses. Indeed, a number of electrophysiological recording and lesion studies in rodents (Lucantonio et al., 2015; Morrison, Saez, Lau, & Salzman, 2011; Roesch, Calu, Esber, & Schoenbaum, 2010; van Wingerden et al., 2010) and primates (Chau et al., 2015; Elisabeth A Murray et al., 2015; West, DesJardin, Gale, & Malkova, 2011) suggest that OFC activity tracks the expected value of cues used to guide behaviour. Therefore, situations in which disruption of OFC function impairs behaviour are likely to indicate deficits in selecting optimal behaviour based on the current motivational values within the array of possible behaviours. This account would explain deficits in inhibitory control as deficits in resolving response competition, and would also account for reports that the OFC is only necessary for modifying established behaviours rather than establishing control of de novo behaviours (E A Murray et al., 2007).

**Outcome expectancy guiding behaviour**

A number of findings in experiment 1 suggest that OFC inactivation disrupted cue guided behavioural control rather than affecting learning per se. OFC inactivation disrupted behavioural control during the A+/AX- discrimination, but did not disrupt learning about the inhibitory properties of cue X (experiment 1). Similarly, OFC inactivation suppressed acquisition to control cue Z. While this effect persisted when OFC was subsequently functional, it also affected control cue B which was not present during OFC inactivation. These findings are consistent with the representation of the value of expected outcomes in the OFC. Specifically, in Pavlovian cue-outcome conditioning the OFC is necessary for using the current motivational value of predicted outcome to guide conditioned behaviour (Gallagher et al., 1999; Pickens et al., 2003; Pickens, Saddoris, Gallagher, & Holland, 2005). In the absence of this information, behavioural control is likely to be guided by direct stimulus-response associations that may form during learning (Delamater, 2007; Hall, 2002; Holland & Straub, 1979; Killcross & Blundell, 2002). Thus, in simple cue-outcome learning to control cue Z, the suppression in response acquisition following OFC inactivation may represent the loss of information about the current value of the reward that normally boosts responding, and a reliance on a slower stimulus-response memory system. Similarly, during the A+/AX- feature negative discrimination the loss of information about the current value of the reward would not be available to boost responding to A+. However, an inhibitory association between X and responding (or an excitatory connection between X and a specific representation of no-outcome (Delamater, 2004; Konorski, 1967)) could still form with only a stimulus-response system. However, while we provide direct evidence that learning of conditioned inhibition is not disrupted by OFC inactivation, further evidence is required to test whether behaviour, but not learning, is disrupted during simple cue-outcome learning.

This outcome expectancy view can also account for deficits in outcome devaluation following disruption of OFC function. In rats and monkeys, disruption of OFC function blocks the appropriate reduction in responding for a predicted reward that is no longer rewarding (Gallagher et al., 1999; Pickens et al., 2003; West et al., 2011). Indeed, this effect is still reported when OFC function is disrupted immediately prior to test but after initial learning and the outcome has been devalued (Elisabeth A Murray et al., 2015; Pickens et al., 2005). This suggests that the OFC is involved in accessing the current value of expected outcomes and appropriately guiding behaviour rather than learning about changes in outcome value. Furthermore, in the rat this effect appears to be restricted to Pavlovian cue-outcome behaviour and not instrumental action-outcome behaviour (Balleine, Leung, & Ostlund, 2011; Ostlund & Balleine, 2007).

**Outcome expectancy for learning**

We have previously shown that the OFC is necessary for learning about cues that no longer signal reward in extinction procedures (Panayi & Killcross, 2014). The present findings (experiment 2) extend this to show that the specific extinction procedure parameters employed do not generate significant conditioned inhibition to other cues, and that OFC is not necessary for inhibitory cue-outcome learning in general. These findings are problematic for a strict view in which the OFC is the neural locus of outcome expectancy information that is involved in computing prediction errors necessary learning. From a theoretical perspective, outcome expectancy information is a necessary component for prediction error signals which are critical to learning in associative learning (Mackintosh, 1975; Pearce & Hall, 1980; Rescorla & Wagner, 1972) and reinforcement learning theories (Sutton & Barto, 1998). Prediction errors are calculated as the discrepancy between the expected value and the actual-experienced value of an outcome. Learning can therefore be described as a process of incrementally minimising errors in prediction. Prediction error signals have been identified in the firing of mid-brain dopamine neurons (Hollerman & Schultz, 1998; Schultz, 1998) and have been causally linked to learning (Steinberg et al., 2013). Therefore, a straightforward prediction of the view that the OFC represents outcome expectancy signals that inform prediction errors is that disrupting OFC function should disrupt mid-brain prediction error signalling and fundamentally disrupt learning. However, this is refuted by a number of reports that OFC lesions do not disrupt initial task learning (Boulougouris, Dalley, & Robbins, 2007; Chang, 2014; Gallagher et al., 1999; Ostlund & Balleine, 2007; Scarlet, Delamater, Campese, Fein, & Wheeler, 2012), and do not disrupt putative reward prediction errors signals in the VTA in a manner consistent with the loss of outcome expectancy information (Takahashi et al., 2011).

To account for intact initial learning of tasks following OFC damage, current theories of OFC function (Delamater, 2007; Rudebeck & Murray, 2011; Schoenbaum et al., 2009) appeal to the distinction between learning about different aspects of rewards such their sensory specific properties (e.g. taste, shape, colour, location etc.) and their general motivational and rewarding properties (Dickinson & Dearing, 1979; Wagner & Brandon, 1989). The OFC is argued to represent outcome expectancy information about the sensory specific properties of outcomes, leaving learning about the general properties of rewards intact and capable of supporting acquisition in the absence of OFC function. However, when correct task performance depends the task depends on representing the specific properties of the outcome, such as when a specific outcome is devalued, then OFC function is necessary for correct performance (Gallagher et al., 1999; Elisabeth A Murray et al., 2015; West et al., 2011). However, this explanation does not account for deficits in extinction learning in which the specific properties of the outcome are not relevant to task performance (Panayi & Killcross, 2014). Instead, (Panayi & Killcross, 2014) hypothesised that the disruption of expected outcome value information reduced the motivational significance of the extinction session in which no rewards were delivered. Consequently, responding at the start of the session may be driven by stimulus-response associations, but the lack of motivationally significant events in the chamber may facilitate rapid habituation to the cue and the context, protecting the responding from substantial extinction learning. This is supported by evidence of rapid within-session extinction found by (Panayi & Killcross, 2014) which was replicated in experiment 2, and has been reported before (see figure 3E in (Keiflin, Reese, Woods, & Janak, 2013)). Indeed, the increased number of non-rewarded trial types in experiment 2 may account for the clearer evidence of rapid within-session extinction compared to that originally reported by (Panayi & Killcross, 2014).

A more recent approach has been to associate OFC function with model-based reinforcement learning (Keiflin et al., 2013; M. A. McDannald et al., 2011; M. McDannald et al., 2012; Takahashi et al., 2011; Wilson et al., 2014). Similar to the sensory-specific/general-motivational distinction, reinforcement learning distinguishes between model-based, sensory rich learning about task structure and specific reward properties, and model-free, general learning about non-specific average reward rates associated with cues or actions (Daw, Niv, & Dayan, 2005). The possibility that the OFC is involved in model-based learning extends the scope of OFC function to include representing task structure as well as specific properties of outcomes.

Recently (Wilson et al., 2014) have modelled deficits in extinction following OFC damage as a deficit in representing a change in the task based on latent information such as associative history rather than explicit environmental cues. Therefore, with an intact OFC, subjects detect that the rate of reinforcement has changed during an extinction session and create a new task state representation in which new context-specific inhibitory learning can be acquired. In the absence of a functioning OFC, the subject cannot use internal information about the associative history of the cue to generate this new task state, and instead must directly update the original acquisition memory. Therefore, extinction learning in the absence of OFC function is modelled as erasure of the original learning rather than new context specific inhibitory learning. However, the present findings showing that OFC inactivation increases the rate of within-session extinction and disrupts between session extinction do not fit this model. Furthermore, the disruption of discriminative behaviour during the A+/AX- discrimination is at odds with the model which predicts that the availability of external cues, such as the physical presence of cue X in the AX- compound, should not be dependent on the OFC.

One possible reason for the discrepancy between the present findings and the model proposed by Wilson et al (Wilson et al., 2014) is the functional heterogeneity amongst the subregions of both the rodent and primate OFC. In particular, the model based simulations of deficits during extinction are modelled on lever responding monkey data from (Butter, Mishkin, & Rosvold, 1963) in which ablations of the entire orbital surface were conducted. Therefore it is likely that the model accounts for a range of OFC functions across multiple orbital regions (Bradfield, Dezfouli, van Holstein, Chieng, & Balleine, 2015; Sharpe, Wikenheiser, Niv, & Schoenbaum, 2015).

There are a number of diverse regions that have uniformly been considered as OFC regions (Price, 2006a; Roesch & Schoenbaum, 2006), however there is mounting evidence that these subregions are functionally heterogeneous in rodents and primates (Balleine et al., 2011; Mar, Walker, Theobald, Eagle, & Robbins, 2011; Rudebeck & Murray, 2011; Mark E Walton et al., 2015). In the present experiments cannula tips were restricted to the anterior portion of the lateral OFC. This is in contrast to the majority of rodent OFC studies that target the posterior portion of the lateral OFC with cannulae and neural recording probes, or excitotoxic lesion studies that can encompass lateral OFC, ventral OFC and agranular insular cortex (Chudasama & Robbins, 2003; Gallagher et al., 1999; Pickens et al., 2005; Scarlet et al., 2012). Rodent ventral and lateral OFC are functionally dissociable from the medial OFC (Mar et al., 2011), and ventral OFC appears dissociable to lateral OFC (Balleine et al., 2011; Corwin, Fussinger, Meyer, King, & Reep, 1994). Furthermore, these orbital subregions have distinct patterns of connectivity within the medio-dorsal thalamus, amygdala, and striatum in both rodents and monkeys (Groenewegen & Uylings, 2000; Hoover & Vertes, 2011; McDonald, 1998; Price, 2006b; Schilman et al., 2008). Functional heterogeneity in primates has also been shown between Walker’s areas 11, 12 and 13 (Elisabeth A Murray et al., 2015; Noonan et al., 2010; Rudebeck & Murray, 2011; M E Walton, Behrens, Buckley, Rudebeck, & Rushworth, 2010). It is therefore important to start discriminating between OFC subregions when characterising the function of the OFC and attempting to establish homologous regions between species and clarify inconsistent findings.

**Summary**

* Describe outcome expectancy hypothesis
  + Argue that there are 2 variants: Involved in prediction errors vs only involved in behavioural control
    - VTA signalling, schoenbaum/takahashi papers; Over-expectation
  + Extinction study provided a test of this hypothesis
    - Supports a role in signalling negative prediction error
    - Replication in this study -> also tested whether the parameters used were likely to generate inhibition to incidental cues -> Not the case
    - Similarly, the finding that conditioned inhibition was acquired (although not expressed) during OFC inactivation suggests that the impairment in extinction is not the result of disrupting negative prediction error signalling!
    - This was also the conclusion argued in the original extinction paper based on the existence of intact (and potentially accelerated) within-session extinction. Instead, the impaired extinction was argued to be the result of a protection from extinction process caused by rapid habituation to the CS following the disruption of the expected value of the outcome.
* Disruption of acquisition -> once again, supports outcome expectancy function of OFC, however this time it would suggest that acquisition learning was disrupted, i.e. positive prediction errors? However, this conclusion requires further testing because performance levels may reflect altered learning or altered behavioural expression (which is suggested by the transient suppression of responding to cue B+ (stage 3; Experiment 1) even though initial training in stage 1 was drug free and cue B was never presented during drug infusions in stage 2.

**Performance vs. learning**

* Janak hierarchical
* Wilson latent states model
* Support for dissociable roles in performance vs learning can be found in Murray et al (2015) deval paper [also allows for the discussion of primate-> rodent homology]

To test whether deficits in extinction learning following OFC inactivation are due to disrupting the acquisition of conditioned inhibition, we used two procedures to establish inhibition to a novel cue. We found that, compared to control infusions of saline, OFC inactivation via infusions of muscimol reliably disrupted the retention of extinction learning between sessions while increasing the rate of extinction within sessions. Furthermore, when extinction of a different predictive cue occurred in compound with a novel cue, regardless of OFC function during the extinction phase, rats did not readily acquire inhibitory properties to the novel cue as assessed by a retardation test. This suggests that the parameters used in this procedure did not reliably promote the formation of conditioned inhibition between incidental cues and the outcome. OFC inactivation during a feature negative discrimination procedure designed to reliably produce conditioned inhibition did not affect the formation and subsequent expression of conditioned inhibition as assessed by both a summation and retardation test of inhibition. However, discriminative behavioural control during the feature negative discrimination was abolished following OFC inactivation which resulted in similarly low levels of responding to all of the cues presented. Surprisingly, the suppression of responding to the control cue during OFC inactivation persisted on subsequent training sessions in the absence of infusions. These findings extend our understanding of the role of the OFC in reward guided behavioural control and have implications for the current dominant theories of OFC function.

**OFC is not necessary for the learning of conditioned inhibition**

* Consistent with findings that the OFC is not required for novel learning, especially when changes in task demands are explicitly signalled by cues (c.f. Wilson et al)

**OFC inactivation disrupts the expression of conditioned inhibition**

Impairments to appropriate behaviour following inactivation or lesions of the OFC normally results in a failure to suppress or reduce inappropriate behaviour {Reversal, Devaluation, Extinction}. In the present study, OFC inactivation disrupted the expression of selective inhibition during a feature negative discrimination

* OFC inactivation abolishes discriminative responding (i.e. selective behavioural inhibition)
* Papers looking at discrimination learning (5-CSRRT?) -? Similar?

OFC inactivation disrupts between- but not within-session extinction

OFC inactivation suppresses acquisition behaviour

*OFC modulates behaviour based on the current value of expected outcomes*

**Over-expectation papers**? The failure to disrupt new inhibitory learning in the present experiments is not consistent with these findings. However, the persistent suppression to cue Z is similar to the findings of over-expectation experiments. However, it is not clear if the suppression observed here is necessarily due to impairments in learning or merely behavioural suppression… something that applies equally to the overexpectation results.

* In terms of explanations using the Wilson model, it is not clear how the model would account for the suppression in behaviour seen during normal acquisition… Doing so would have to concede that continued acquisition (sub-asymptotic) requires the mental simulation of hidden states… This throws out all the other unique predictions made by this model
* Furthermore, the failure to account for the extinction results replicated here is in direct opposition the explicitly predicted results!

Solution, the function of the OFC is not described by this model, it may describe other parts of the OFC (Cite Mel’s Neuron commentary …. ?).

**Credit assignment?** It would seem that poor credit assignment could account for the overall suppression in performance found in the muscimol group, this could be a misattribution of the non-rewarded trials to cue A… This account fits nicely with the infusion data, but not with the intact acquisition of conditioned inhibition when tested drug-free which suggests unimpaired credit assignment during this learning period.

Interaction between OFC and other neural circuits

* (Keiflin et al., 2013) – Hierarchical view
  + Placements were accurately within LO, a bit more posterior i.e. focussed around +3.70
  + Expt 1b. extinction test – inactivation resulted in rapid extinction as measured by # f trials initiated
  + Impaired responding to cue Z persists when tested drug free on the following day unlike the hierarchical results found in kieflin et al
    - Similarly, extinction to cue C (replicating Panayi & Killcross…) retained deficits from stage 2 when tested drug free
    - Unfortunately, it is not clear how long term the deficits in Keiflin et al’s experiments are i.e. Figure 6C, there was no test drug free following the second infusion day to see if the MB/MB group retained their preference. Furthermore, both MB groups started at around 0 preference suggesting conflicting response control.
* (Wilson et al., 2014) – Hidden state space view
  + Impoverished extinction between days (cue C) is consistent with the model predictions, except that the model data are based on extinction within session (Butter, 1969; 10 min blocks Fig 3).
  + Another troubling result is the explicitly cued absence of the outcome in the feature negative design i.e. cue X is clearly an explicit rather than a hidden state, yet performance was impoverished throughout OFC inactivation despite the clear cues to help guide behaviour.
* Current outcome value view - (Rudebeck & Murray, 2014; Mark E Walton et al., 2015)
  + Current value of outcome is not available under drug infusions, thus affecting responding but not necessarily affecting learning – other systems? [tie in with hierarchical system view of Keiflin?]
  + A method by which CS representation hangs around in A2 and never returns to I for re-activation to A1 in the presence of the cue
  + Walton experiment with credit assignment -> shows that learning was driven by specific Pavlovian contingencies, however since this was a lesion study it is not clear if this is a disruption of learning or behavioural performance per se.

??? Change entire article to OFC and then discuss functional heterogeneity in the discussion???